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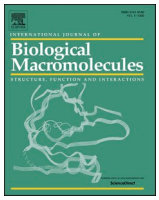

Review

Collagen IV and laminin-1 as key macromolecules in ocular structure and pathology: A review

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ABSTRACT

The extracellular matrix (ECM), particularly the basement membrane (BM), is critical for the structural organization and functionality of ocular tissues. Among its core components, type IV collagen and laminin-1 play central roles in cell adhesion, polarity, differentiation, and survival. These macromolecules are ubiquitously expressed in the cornea, lens, retina, and optic nerve, forming tissue-specific BMs that support development and homeostasis. In this review, findings on the spatial distribution and molecular roles of collagen IV and laminin-1 in the eye under physiological and pathological conditions, are summarized. Mutations in *COL4A1*, *COL4A2*, and laminin-encoding genes (*LAMA1*, *LAMB1*, *LAMC1*) are associated with a range of ocular disorders, including anterior segment dysgenesis, lens dystrophy, optic nerve hypoplasia, and retinal abnormalities. Furthermore, autoimmune responses targeting these BM proteins have been implicated in systemic diseases such as rheumatoid arthritis, systemic lupus erythematosus, systemic sclerosis, and Sjögren's syndrome, often leading to serious ocular complications. This review emphasizes the importance of ECM macromolecules in maintaining ocular integrity and highlights their potential as diagnostic biomarkers and therapeutic targets in both inherited and immune-mediated eye diseases.

1. Introduction

The extracellular matrix (ECM) is a non-cellular structural network that plays essential roles in supporting cells and regulating various cellular processes, including growth, migration, cell-cell interactions, proliferation, homeostasis, morphogenesis, tissue development, and differentiation [1,2]. ECMs are broadly classified into two main types: the interstitial matrix, which surrounds cells within connective tissues, and the pericellular matrix, which is closely associated with the cell surface [3].

The interstitial matrix primarily consists of macromolecules such as collagen type I, fibronectin, elastin, and glycosaminoglycans, all of which contribute to the structural scaffolding and mechanical properties of tissues [4,5]. In contrast, the basement membrane (BM), a specialized form of pericellular matrix, plays a crucial role during development and in tissue homeostasis. It regulates cell polarity, provides structural support, and acts as a semi-permeable barrier in various tissues. The major molecular components of the BM include collagen type IV, laminin-1, perlecan, and nidogens [6].

It is important to note that the extracellular matrices of ocular tissues largely resemble those of other organs [7]. The ECM in the eye also exists in two general forms: the interstitial matrix found between cells, and the BM located at the interface between epithelial or endothelial cells and the underlying connective tissue.

This review aims to summarize the distribution of two key ECM proteins, collagen IV and laminin-1, across selected ocular structures. Additionally, it highlights eye disorders associated with genetic mutations affecting ECM components, offering insight into the role of ECM dysfunction in ocular pathology.

2. Extracellular matrix proteins: collagen IV and laminin-1

2.1. Type IV collagen

Type IV collagen (Fig. 1) is a family of complex polypeptides and a major structural component of BMs. In mammals, six distinct α chains of type IV collagen, designated α1(IV) through α6(IV), have been identified [8]. These chains assemble into three different heterotrimeric isoforms with specific tissue distributions.

The classical $\alpha_1\alpha_1\alpha_2$ heterotrimer is the most ubiquitous, present in nearly all embryonic and adult BMs. The $\alpha_3\alpha_4\alpha_5$ isoform is found predominantly in specialized BMs, such as those of the kidney glomerulus

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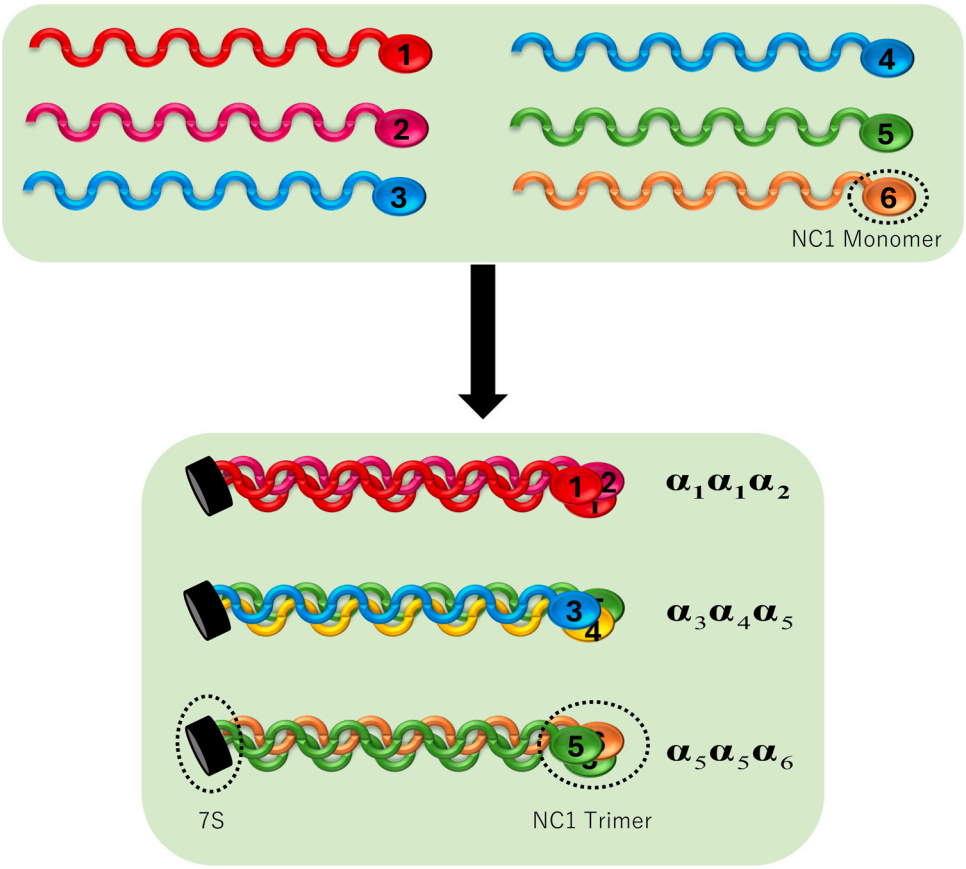

Fig. 1. The type IV collagen consists of three distinct α-chains: $\alpha_1\alpha_1\alpha_2$, $\alpha_3\alpha_4\alpha_5$ and $\alpha_5\alpha_5\alpha_6$. These chains are encoded by 6 different genes: (α1(IV), α2(IV), α3(IV), α4 (IV), α5(IV), and α6(IV)). All type IV collagen α chains contain an N-terminal 7S domain, a central collagenous triple helix domain, and a C-terminal noncollagenous (NC1) domain.

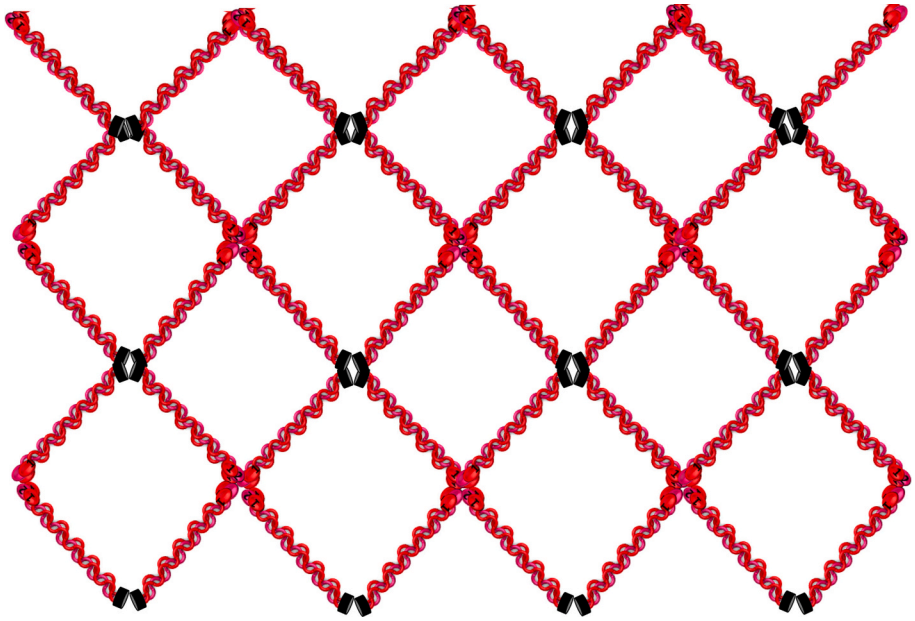

Fig. 2. Model for the assembly and network organization of collagen iv protomers. Collagen iv protomers assemble through specific end-to-end interactions at their n-terminal 7 s domains and c-terminal nc1 domains, forming a stable, interconnected meshwork. Lateral associations along the triple-helical domains contribute to the formation of a three-dimensional scaffold, which provides mechanical support and acts as a platform for the binding of other basement membrane components.

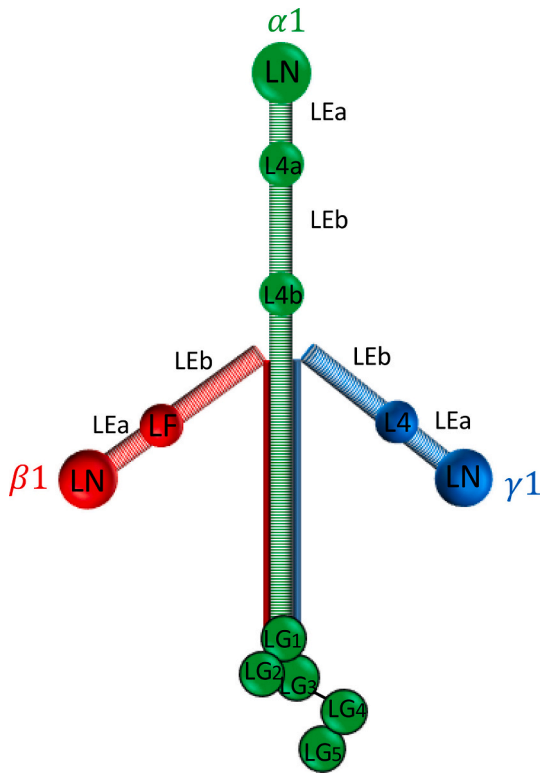

fig. 3. A schematic representation of the laminin-1 molecule. The laminin-1 structure is composed of three subunits, α, β, and γ. LN, laminin N-terminal domain; LE (laminin-type epidermal growth (EGF) factor-like); laminin 4 (L4 for laminin α and γ chains, and LF for laminin β chain) domain; a large COOH-terminal globular (G) domain with five internal repeat motifs (LG1–LG5).

[9], pulmonary alveoli [10], inner ear cochlea [11], and ocular tissues [12]. The third isoform, $\alpha_5\alpha_5\alpha_6$, involves α5 and α6 chains and is primarily expressed in the BMs of smooth muscle tissues, including the aorta and bladder [13], as well as in the skin [14], and Bowman's capsule [15], among others.

Each α chain consists of three main domains: a short N-terminal 7S domain, a long central collagenous domain with repeating Gly-X-Y sequences, and a non-collagenous C-terminal globular domain (NC1) [8]. Notably, NC1 domains have been implicated in anti-tumour and anti-angiogenic activities [16–18], highlighting their potential functional significance beyond structural roles.

Once secreted into the ECM, type IV collagen protomers self-assemble into a specialized, fine mesh-like network [19] that supports epithelial and endothelial cells and acts as a selective barrier between tissue compartments [20]. This network is formed through specific end-to-end interactions at both termini of the protomers, creating two key structural junctions (see Fig. 2). At the C-terminal, the non-collagenous (NC1) domains of two protomers interact to form an NC1 hexamer, a structure stabilized by sulfilimine cross-links that enhance the mechanical integrity of the network [21]. At the N-terminal, four 7S domains associate to form a 7S dodecamer, which is further stabilized by aldehyde-derived cross-links, contributing additional strength and resilience to the BM [22].

2.2. Laminin-1

Laminins are a family of ECM glycoproteins and represent the predominant non-collagenous proteins within the BM. To date, more than 15 laminin isoforms have been identified, each formed by a unique trimeric assembly of three distinct subunits: α, β and γ chains [23]. The first and most extensively studied isoform, laminin-1, is composed of the α_1, β_1 and γ_1 chains (Fig. 3) and was originally isolated from the Engelbreth-Holm-Swarm (EHS) mouse tumour matrix [24].

A defining characteristic of all laminin α-chains is the presence of a large C-terminal globular (G) domain, which is subdivided into five distinct LG domains (LG1–LG5) [25]. The short arms of laminin-1 share homologous structures, including a distal laminin N-terminal (LN) domain that is essential for laminin polymerization and BM assembly [26,27], as well as a less conserved globular L4 domain present in the α and γ chains. Following the LN domain, the chains contain long tandem repeats of laminin-type epidermal growth factor-like (LE) domains interspersed with additional globular domains [28].

Laminins are multifunctional ECM glycoproteins that play critical roles in cell adhesion, differentiation, migration, and maintenance of cellular phenotype, while also conferring resistance to apoptosis [29]. Like type IV collagen, laminins self-assemble into intricate networks (Fig. 4).

Specifically, laminin-1 and collagen IV form two independent supramolecular networks that are interconnected and stabilized by bridging molecules such as nidogen and perlecan, collectively constituting the BM [30–32]. Together, these components self-organize into a three-dimensional matrix that provides essential structural support, protection, and signalling functions [33], (Fig. 5).

Collagen IV and laminin-1 not only provide structural support within the ocular basement membrane but also actively modulate cell behaviour through their interaction with key growth factor signalling pathways, including TGF-β (Fig. 6). These interactions influence lens epithelial cell proliferation, migration, and differentiation, as well as retinal morphogenesis during eye development. TGF-β is synthesized as pre-pro-TGF-β, which, following cleavage of its N-terminal signal peptide, is converted into pro-TGF-β. Within the endoplasmic reticulum, pro-TGF-β molecules dimerize and form disulfide bonds with latent TGF-β binding proteins (LTBPs), generating a ternary complex. This complex is transported to the Golgi apparatus, where pro-TGF-β is cleaved from its pro-peptide to release the TGF-β–latency-associated peptide (LAP) complex, forming the small latent complex (SLC).

Once secreted, TGF-β remains in a latent, inactive form complexed with LAP and LTBP. The LTBP anchors the latent complex to extracellular matrix (ECM) components facilitating its spatial regulation. In ocular tissues, collagen IV and laminin-1 also contribute to TGF-β activation by interacting with integrins, which transduce mechanical and biochemical cues from the ECM to the cell surface.

Various physiological factors, including proteases, thrombospondin-1, reactive oxygen species, and lactic acid, participate in the activation of latent TGF-β, releasing the mature cytokine. Once activated, TGF-β binds to its type II and type I receptors, initiating phosphorylation of downstream SMAD2/3 proteins, which subsequently complex with SMAD4 and translocate to the nucleus to regulate gene expression. This signalling cascade governs cell proliferation, migration, and differentiation, processes that are fundamental to retinal morphogenesis, lens development, and overall ocular tissue homeostasis.

In this context, the coordinated interactions between collagen IV, laminin-1, and integrins are essential for modulating TGF-β bioavailability and signalling dynamics within the ocular microenvironment.

3. Distribution of type IV collagen and laminin-1 in normal ocular tissues

3.1. The cornea

The cornea is a resilient and transparent tissue responsible for refracting and transmitting light onto the lens, which subsequently focuses it onto the retina. Together, the cornea and lens provide approximately two-thirds of the eye's total refractive power [34]. Structurally, the cornea consists of five distinct layers (Fig. 7): the epithelium, Bowman's layer, stroma, Descemet's membrane, and endothelium.

Immunohistochemical studies have shown that both corneal

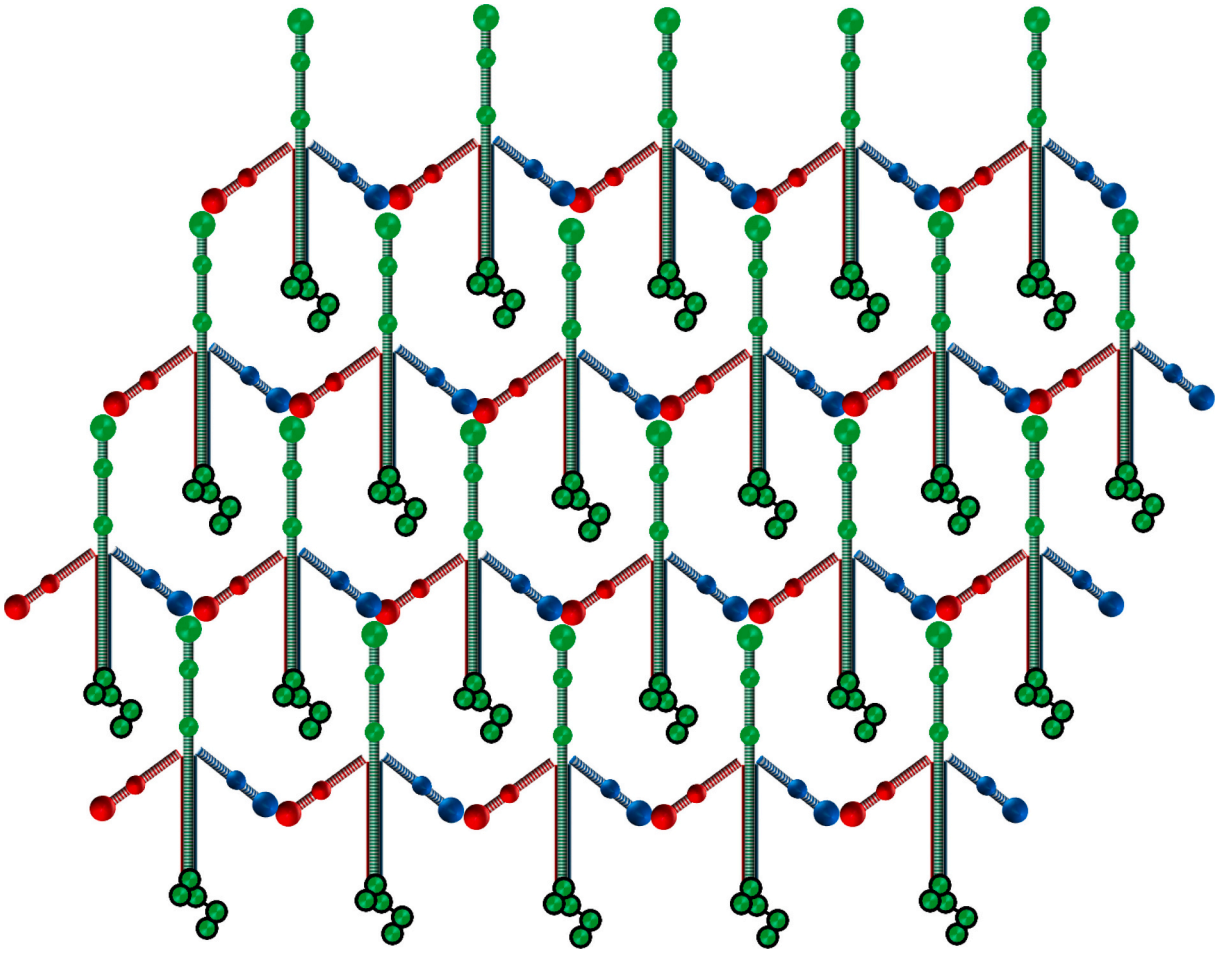

Fig. 4. Schematic drawing of the laminin-1 self-assembly.

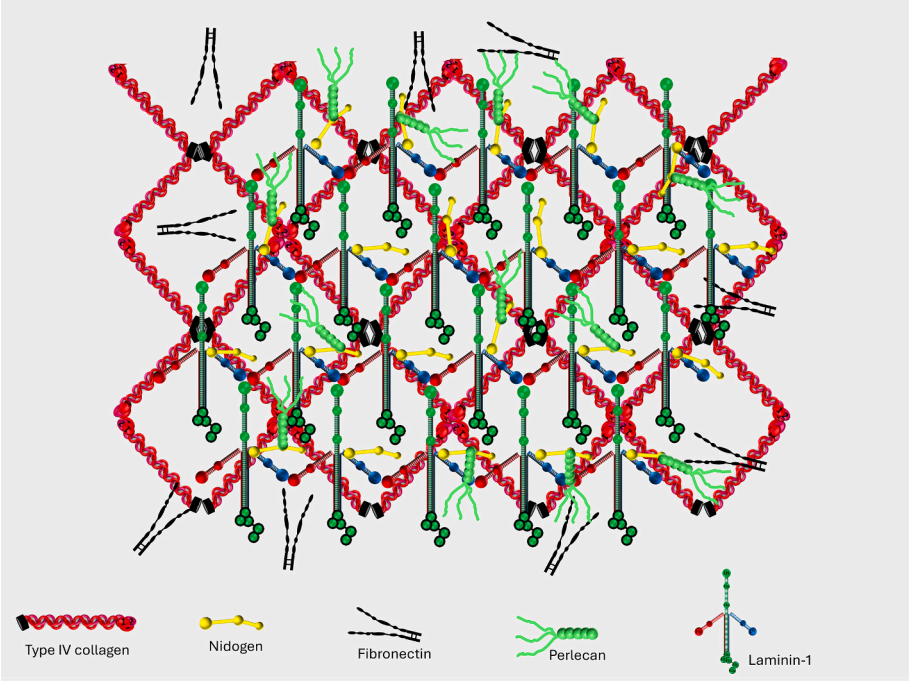

Fig. 5. Schematic diagram showing the molecular structure of a basement membrane.

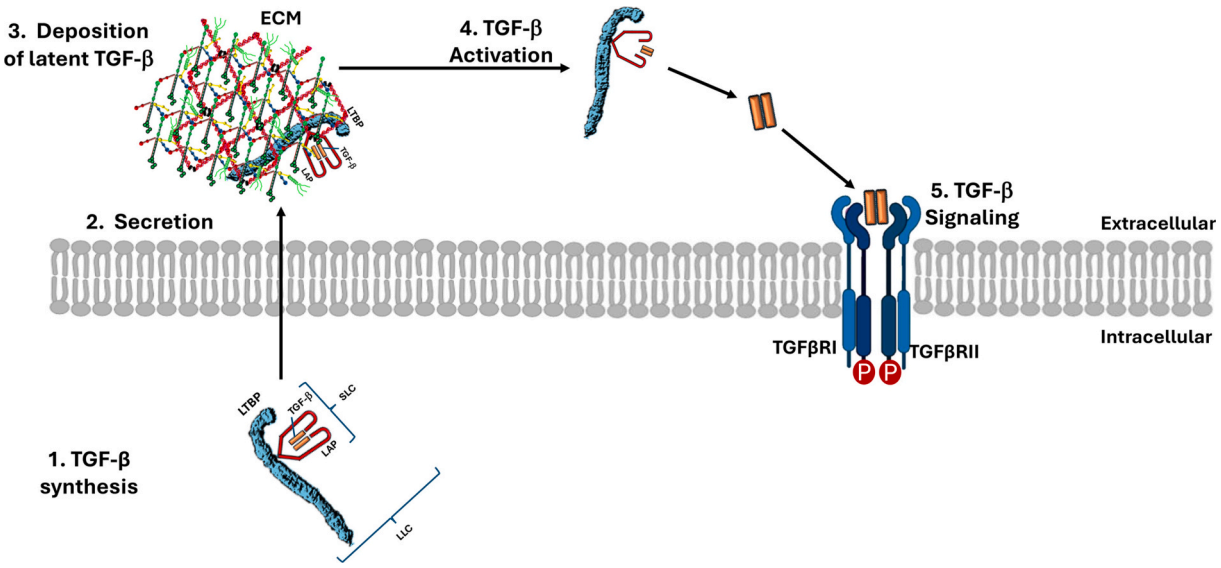

Fig. 6. Graphical summary of TGF-β protein production, secretion, ECM deposition, and activation.

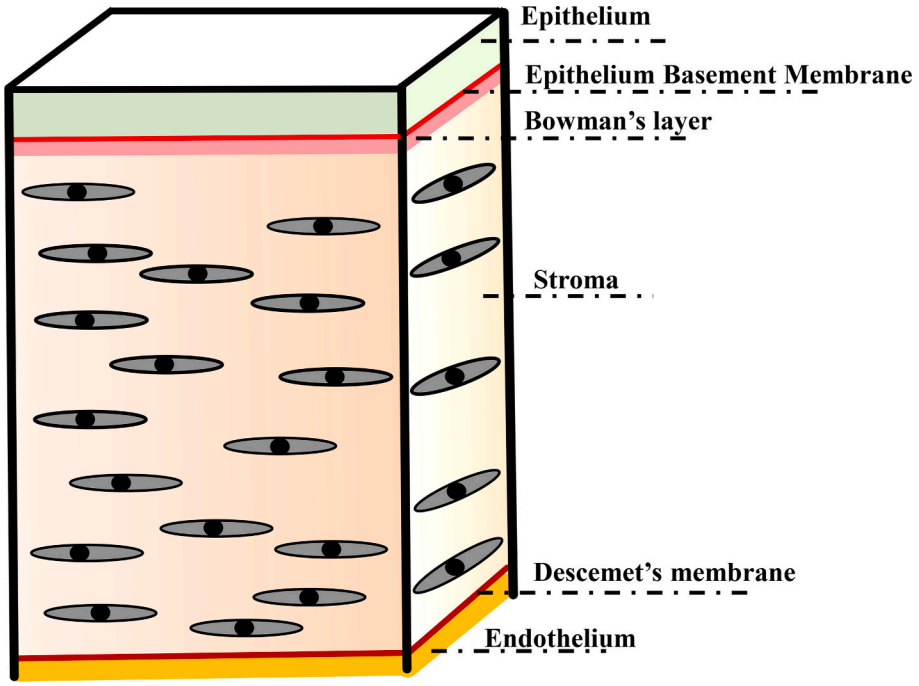

Fig. 7. A schematic illustration of the corneal layers.

epithelial cells and stromal keratocytes synthesize major BM components, including collagen IV and laminin-1 [35]. Multiple investigations have demonstrated the presence of type IV collagen within the corneal stroma, Bowman's membrane, epithelial and endothelial BMs, Descemet's membrane, and around corneal nerves [36–39]. In contrast, laminin-1 is predominantly localized in the epithelial BM, corneal fibroblasts [40,41], and along the endothelial surface of Descemet's membrane [42].

3.2. The lens

The lens of the eye is situated posterior to the cornea and iris. It is a transparent, biconvex structure that allows light to pass through and focus precisely onto the retina. Along with the cornea, the lens contributes to the eye's transparency and refractive power, two essential biophysical properties necessary for proper vision [43]. Anatomically, the lens is composed of three main components: the lens capsule, the lens epithelium, and the lens fibres (Fig. 8). The lens epithelium is divided into three distinct regions along the anteroposterior axis: the anterior central zone, the germinative zone, and the transition zone [44]. Cell proliferation is relatively low in the anterior central zone, whereas it is most active in the germinative zone, located just anterior to the lens equator. Beyond the equator lies the transition zone, where epithelial cells begin differentiating and elongating into fibre cells [45].

Within the lens, both epithelial and fibre cells synthesize and secrete collagen IV and laminin-1, which are essential for the development and maintenance of the anterior, posterior, and equatorial regions of the lens capsule [46]. The lens capsule not only provides structural support, anchoring the lens within the eye, but also serves as a basal attachment site for epithelial cells. This anchorage is crucial, as it delivers signals

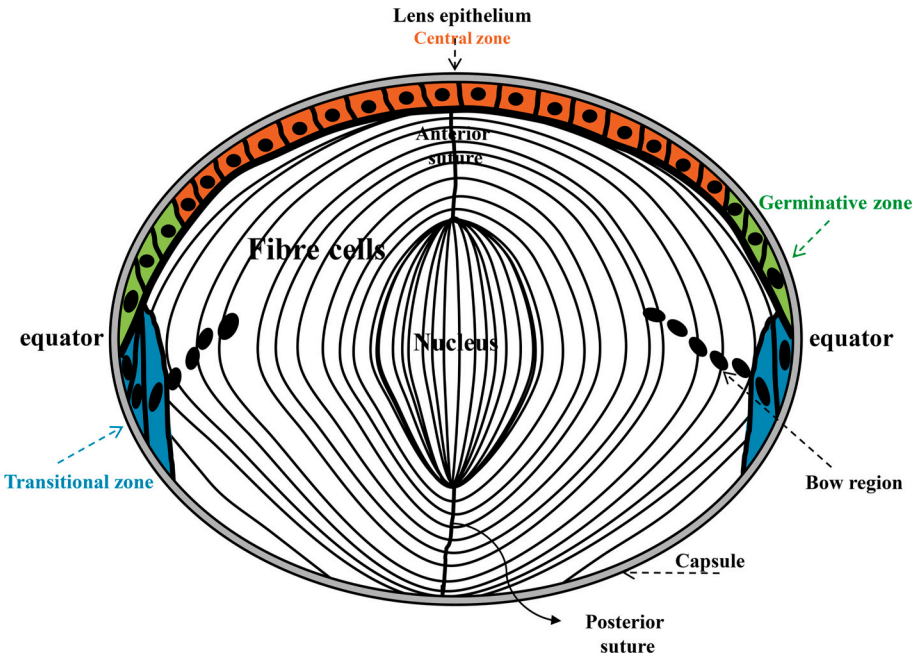

Fig. 8. Diagrammatic cross-section of ocular lens regions.

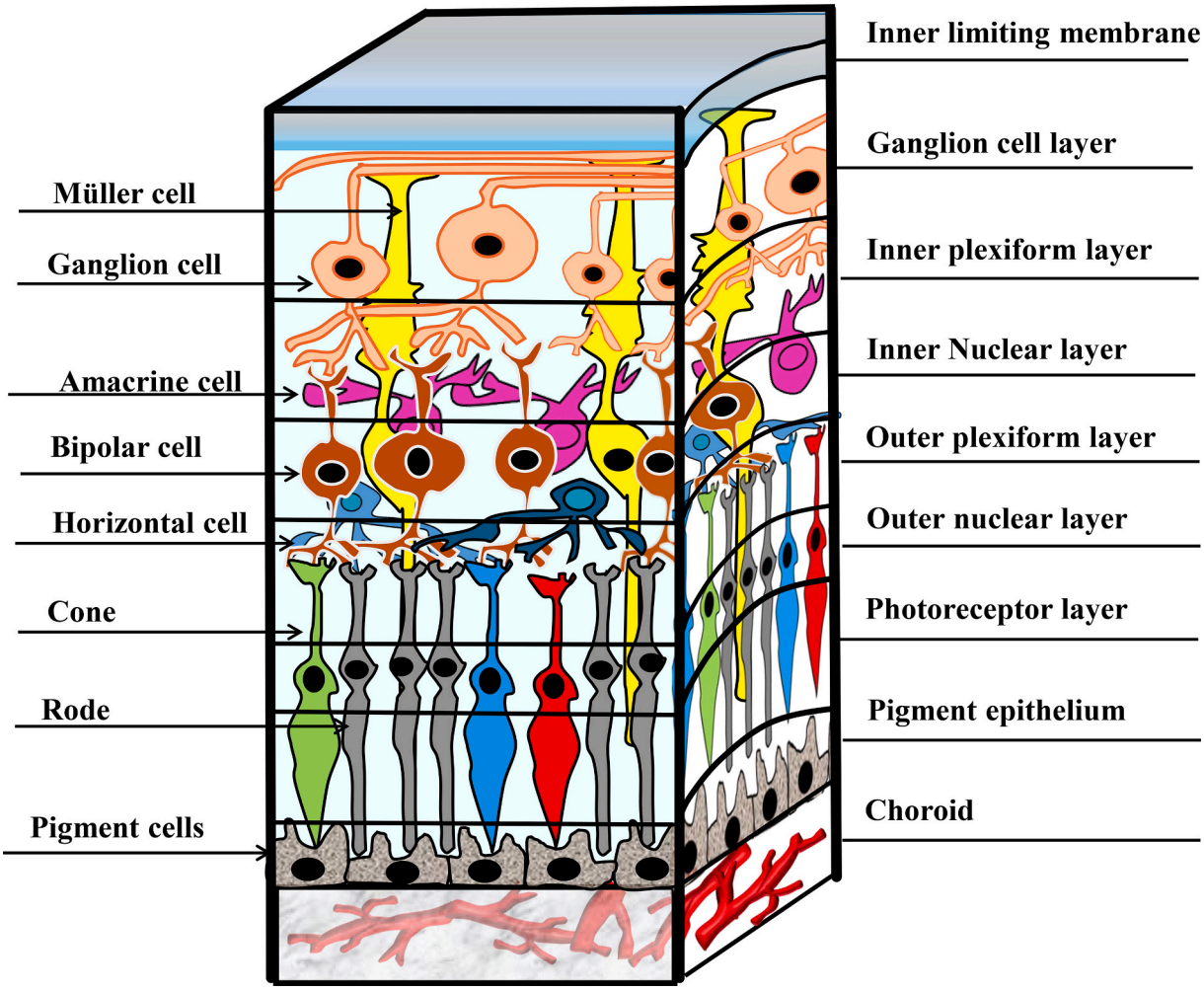

Fig. 9. Schematic representation of a cross-section of the retina showing the spatial arrangement of the neuronal cell layers.

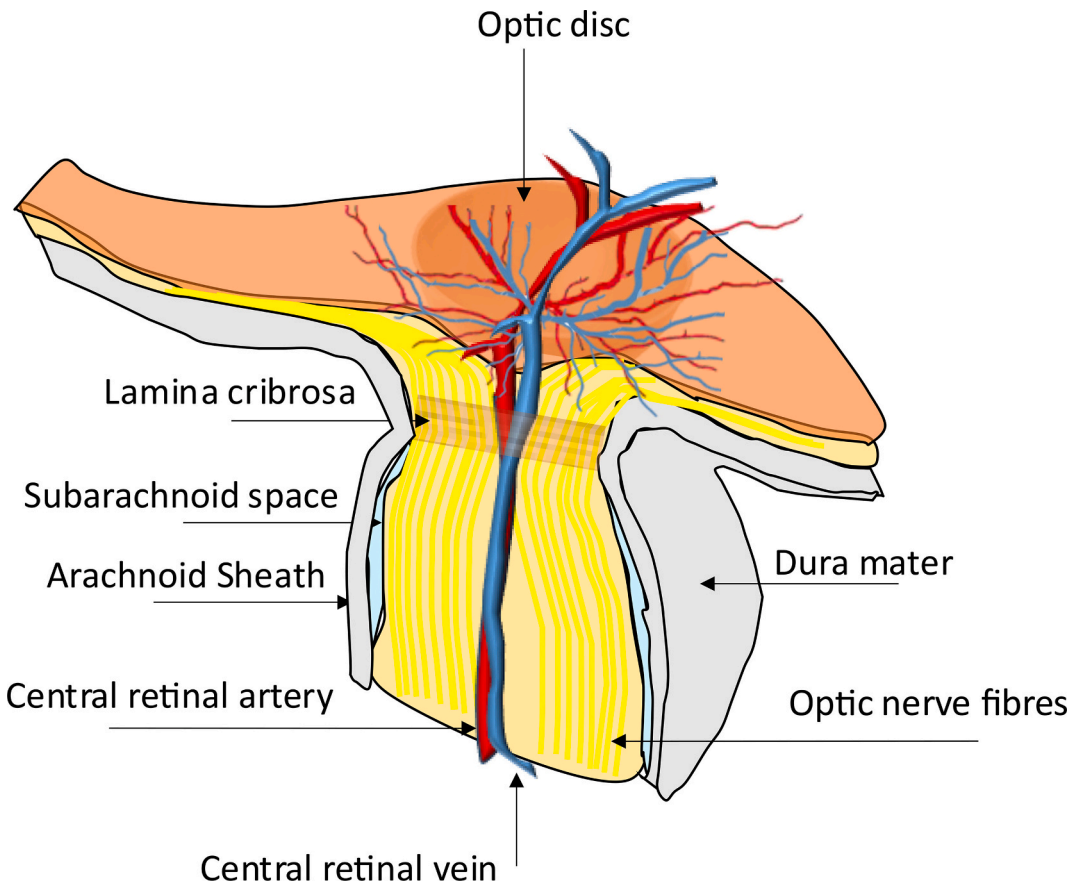

Fig. 10. Schematic drawing illustrating the optic nerve.

necessary for proper lens cell proliferation, migration, and differentiation [47,48]. Moreover, the lens capsule functions as a selectively permeable barrier, separating the lens from the surrounding ocular environment [49]. This protective role helps shield the lens from bacterial invasion and most viral infections [50].

3.3. The retina

The retina is a specialized extension of the central nervous system responsible for detecting incoming light and converting it into neural signals that are transmitted to the brain [51]. It is organized into multiple layers composed of distinct types of neurons interconnected by synapses (Fig. 9). The retina contains three layers of neuronal cell bodies: the ganglion cell layer (GCL), the inner nuclear layer (INL), and the outer nuclear layer (ONL), which are separated by two synaptic layers, the inner plexiform layer (IPL) and the outer plexiform layer (OPL). Photoreceptors, responsible for capturing light, reside in the most apical layer, the ONL. The INL houses interneurons, including bipolar, horizontal, and amacrine cells, distributed along its apico-basal axis. The innermost layer, the GCL, contains the cell bodies of retinal ganglion cells as well as displaced amacrine interneurons.

The inner boundary of the neural retina is defined by the inner limiting membrane (ILM), a specialized BM predominantly composed of collagen IV and laminin-1. The ILM is formed by the end feet of Müller glial cells, which play crucial roles in maintaining retinal homeostasis [52]. Müller cells synthesize ECM components, including collagen IV, which are naturally present in the vitreous, ILM, and retina [53]. In vitro studies have shown that laminin-1 promotes Müller cell migration and enhances the dynamic formation and retraction of their cellular processes [54].

In addition to Müller cells, retinal pigment epithelium (RPE) cells also secrete type IV collagen and specific laminins such as laminin-1 [55,56]. Campochiaro et al. [57] demonstrated the presence of collagen IV and laminin-1 in Bruch's membrane and in the ECM surrounding human RPE cells.

Laminins play key roles in central nervous system (CNS) development [58], a function that extends to the retina, which is considered part of the CNS. Laminin-1 is found in multiple retinal layers, including the ILM, inner nuclear layer (INL), and ganglion cell layer (GCL) [59]. It is essential for guiding retinal ganglion cell axons as they exit the retina and for promoting axonal growth along the optic pathway [60]. Furthermore, genes encoding laminin subunits, Lamc1 (γ1) and Lamb1 (β1), are critical for photoreceptor morphogenesis and synapse formation [61].

During retinal development, collagen IV is present within the interstitial ECM of the neuroblastic cell layer [62]. Both collagen IV and laminin-1 are also found in the BMs of retinal vasculature and the choriocapillaris [59,63].

3.4. The optic nerve

The optic nerve (Fig. 10), also known as the second cranial nerve, is responsible for transmitting visual information from the retina to the brain and is considered an integral part of the central nervous system (CNS). It is formed by the axons of retinal ganglion cells, which converge at the optic disc, also called the optic nerve head, where they bundle together and pass through the fenestrations of the lamina cribrosa. This region marks the point where optic nerve fibres pierce the sclera and are redirected posteriorly to form the orbital segment of the optic nerve [64].

The optic nerve is enclosed by a thick, fibrous sheath called the dura mater, continuous with that of the brain, allowing the free flow of

cerebrospinal fluid between the eye and the intracranial space [64,65]. The subarachnoid space surrounding the brain and spinal cord also extends along the optic nerve [66]. At the centre of the normal optic disc lies a small, pale, whitish depression known as the physiological cup.

The central retinal artery travels within the optic nerve and emerges at the optic disc, where it branches into superior and inferior divisions. This artery supplies oxygen and nutrients to the inner retina and the surface of the optic nerve; thus, occlusion at this level leads to vision loss in the corresponding visual field. Venous blood is collected by the central retinal vein, which follows the same anatomical path as the central artery [67].

The ECM of the optic nerve is primarily synthesized by astrocytes [68]. Multiple studies have detected collagen IV and laminin-1 localized within the pores of the lamina cribrosa, the region through which retinal ganglion cell (RGC) axon bundles exit the eye, with these proteins being produced by astrocytes [69–71]. Additionally, collagen IV and laminin-1 are found in the BMs of astrocytes situated between the laminar beams and lining the optic nerve septa and pia mater [70]. This distribution suggests that collagen IV contributes significantly to the structural integrity and strength of the optic nerve head by supporting the axons as they traverse the posterior wall of the eye [72]. Moreover, these BMs are associated with capillary endothelial cells within the laminar beams as well as with the astrocytes that line these beams [70].

Previous investigations have also identified laminin-1 in the normal optic nerve. Evidence indicates that both RGC axons [73,74] and glial cells [75] express laminin-1 along the optic nerve, playing a key role in guiding axonal projections [75,76].

Finally, all collagen IV chains are expressed in other ocular structures such as the pigmented epithelium of the iris and ciliary body, as well as the trabecular meshwork [38].

Beyond their anatomical distribution in ocular tissues, the interplay between collagen IV and laminin-1 is crucial for maintaining basement membrane integrity and regulating tissue-specific processes. Collagen IV provides the structural framework that confers biomechanical stability, while laminin-1 mediates cell–matrix interactions through integrins and other surface receptors, regulating adhesion, migration, and differentiation.

In the cornea, this interaction preserves tissue transparency and structural integrity: laminin-1 supports epithelial cell adhesion and migration, while collagen IV reinforces the underlying membrane, ensuring mechanical stability during wound repair and epithelial turnover. In the retina, collagen IV forms the core network of the inner limiting membrane, supporting retinal cell organization and survival, whereas laminin-1 helps maintain the blood–retina barrier and facilitates communication between endothelial and glial cells. Together, they ensure both structural support and selective permeability within retinal microvasculature.

Within the lens, collagen IV and laminin-1 cooperate in the lens capsule to preserve elasticity and transparency and sustain epithelial cell differentiation, a balance essential for lens shape and optical quality. Beyond structural roles, these macromolecules coordinate cellular responses during ocular wound healing and tissue remodelling. Following corneal or retinal injury, they function as dynamic signalling platforms guiding epithelial and endothelial migration, proliferation, and differentiation. Disruption of their interaction, as seen in certain genetic or autoimmune disorders, can impair regeneration and promote chronic inflammation or fibrosis. Overall, the functional partnership between collagen IV and laminin-1 extends beyond co-localization, orchestrating both structural support and signalling dynamics critical for ocular basement membrane function.

4. Collagen IV implication in eye diseases

Mutations in type IV collagen genes lead to the intracellular accumulation of mutant proteins due to their failure to be secreted. This accumulation can trigger endoplasmic reticulum (ER) stress and activate the unfolded protein response [77–79]. Mutations in *Col4a1* and *Col4a2* have been linked to a wide range of ocular diseases [80]. Gould et al. [77] demonstrated that *Col4a1* mutations cause ocular Anterior Segment Dysgenesis (ASD), buphthalmos (enlargement of the eyeball), and optic nerve hypoplasia. ASD encompasses several abnormalities, including corneal opacification, pigment dispersion, cataracts, abnormal iris vasculature, persistence of the tunica vasculosa lentis, and severe iridocorneal synechiae. The iridocorneal adhesions obstruct aqueous humour outflow from the anterior chamber, resulting in elevated intraocular pressure in over 50 % of mutant mice.

Additionally, *Col4a1* mutations cause abnormalities in the inner limiting membrane (ILM) and optic nerve hypoplasia, due to a significant reduction in the number of retinal ganglion cell (RGC) axons within the optic nerve, which may predispose to glaucoma. Other glaucoma-related findings include increased collagen IV expression and ECM deposition within the laminar pores, spaces normally occupied by axon bundles, as well as alterations in glycosaminoglycan composition and redistribution of collagen IV within the optic nerve head of glaucomatous eyes [81–84].

Mutations in the *Col4a1* gene are implicated in various ocular anomalies, including corneal opacity, dysmorphic pupils, lens vacuolization, and iridocorneal adhesions [85]. Alavi et al. [86] further described retinal angiomatous proliferation, neovascular lesions, chorioretinal anastomoses, retinal vascular tortuosity, intraretinal lesions, subretinal and sub-retinal pigment epithelium (RPE) fluid accumulation, aberrant vascular remnants within the photoreceptor layer and outer segments, as well as vitreous and subretinal haemorrhages. Favor et al. [87] expanded these findings by documenting ocular phenotypes associated with *Col4a1* and *Col4a2* mutations, such as microphthalmia, corneal thickening, anterior polar opacity with or without corneal-lens adhesions, corneal opacities accompanied by hyperplasia and neovascularization, vacuoles in the secondary fibre cell region, disorganization of the lens epithelial layer, total lens opacification, and vitreous floaters.

Mutations in type IV collagen genes also underlie rare hereditary disorders, including Alport syndrome, characterized by progressive hereditary nephritis, sensorineural hearing loss, and ocular manifestations due to mutations in *Col4a3*, *Col4a4*, and *Col4a5* [88–91].

The pathogenesis involves loss of the mature collagen IV $\alpha_3\alpha_4\alpha_5$ network and persistence of the embryonic $\alpha_1\alpha_1\alpha_2$ network, which culminates in the characteristic clinical phenotype of Alport syndrome [90]. Reported ocular abnormalities include corneal erosions, occasionally associated with epithelial flap detachment and stromal edema [92], anterior lenticonus and cataract [93,94], fleck retinopathy, retinal thinning, macular holes, retinoschisis, vitelliform lesions [95], as well as bull's eye and pigmentary maculopathies linked to abnormalities of the retinal pigment epithelium and Bruch's membrane [96].

Additionally, *Col4a1* mutations have been identified in Walker-Warburg syndrome, a congenital disorder marked by severe cerebral and ocular malformations [97]. Ocular defects associated with this syndrome include retinal dysgenesis, microphthalmia, anterior chamber abnormalities [98], iris hypoplasia, cataracts, persistent primary vitreous, optic disc coloboma, retinal detachment, retinal dysplasia, optic nerve hypoplasia, and glaucoma [99].

5. Laminin-1 implication in eye diseases

Laminin-1 plays a pivotal role from the earliest stages of embryonic development, particularly in ocular morphogenesis. Within the eye, laminin-1 is essential for optic vesicle and optic cup formation [100]. The absence of laminin α1 disrupts multiple steps of optic cup morphogenesis, including optic stalk furrow formation, invagination, and retinal neurogenesis. This is attributed to laminin-1's critical functions in regulating cell survival, migration, morphological remodelling, and maintenance of cell polarity during optic cup development [101].

Mutations in laminin-encoding genes have been implicated in a

Table 1
Summary of collagen iv and laminin-1 mutations, functional impacts, and clinical manifestations in ocular tissues.

Molecule/gene	Ocular tissue	Mutation effect/functional impact	Evidence type	Association/causality	Clinical manifestation
COL4A1	Cornea, Lens, Retina	Disrupts BM structure; weakens cell adhesion	Human studies, animal models	Associative (retinal haemorrhage), Causal (anterior segment dysgenesis in models)	Anterior segment dysgenesis, retinal haemorrhage
COL4A2	Retina, Vasculature	Loss of BM integrity; retinal thinning	Mouse models	Causal	Retinal degeneration, vascular abnormalities
COL4A3 / COL4A4 / COL4A5	Eye (lens, cornea), Kidney	Progressive BM defects	Genetic studies, patient cohorts	Causal	Ocular Alport syndrome: vision loss, corneal opacities, lens subluxation
LAMA1	Cornea	Impaired ECM interactions; disrupted adhesion and migration	Human case studies	Mostly associative	Corneal dystrophy, impaired transparency, vision loss
LAMB1	Retina	Loss of laminin-β1; impaired retinal epithelial function	Animal models	Strong causal evidence	Retinitis pigmentosa, retinal degeneration
LAMC1	Cornea, Retina, Optic nerve	Altered laminin-1 structure; affects adhesion and differentiation	Human studies	Associative	Corneal dystrophy, retinal degeneration, optic neuropathy

spectrum of ocular pathologies. Studies across multiple species have demonstrated that mutations in *lama1*, *lamb1*, and *lamc1* genes impair inner limiting membrane (ILM) formation [102,103], correlating with morphological abnormalities in the ganglion cell layer (GCL) and optic nerve [61,104]. Furthermore, mutations in *lamb1* and *lamc1* result in pronounced photoreceptor dysfunction [61]. Semina et al. [105] reported comparable defects, observing disorganization within the neural retina's GCL, characterized by regional variations in thickness, alongside retinal ganglion cell (RGC) axonal pathfinding errors toward the optic nerve head. Disruptions to the ILM are often concomitant with aberrant retinal vasculature development [102,106]. Notably, *lama1* mutations induce vitreoretinal vascular anomalies, persistence of fetal vasculature, and epiretinal membrane formation. In some mutants, the ILM exhibits fragmentation with frequent discontinuities, permitting Müller glia and ganglion cells to protrude aberrantly into the vitreous cavity [106].

At the retinal level, the *lama1* mutation predominantly affects the ILM and GCL, while sparing other retinal layers. This phenomenon may be due to the limited involvement of laminin α1 chains in outer retinal development and maintenance or compensation by alternative laminin isoforms substituting for the absent laminin α1 chain [61].

Elongating lens fibre cells are known to interact closely with laminin within the lens capsule microenvironment [107]. It has also been established that lens fibre cells form apical, apical contacts with the overlying lens epithelial cells, while the basal surfaces of both cell types interface with the lens capsule [108]. These cell, capsule interactions are critical for proper lens development, fibre cell differentiation, and overall lens morphogenesis [109]. Genetic mutations in the *lama1*, *lamb1*, and *lamc1* genes in zebrafish models have been shown to result in severe lens dysplasia, often leading to capsule rupture. Affected lenses exhibit profound structural disorganization and significant defects in fibre cell differentiation [103,110]. Semina et al. [105] further demonstrated that lama1 mutations result in pronounced lens degeneration, with neither lens epithelial cells nor fibre cells undergoing normal differentiation. In many lama1 mutant models, microphthalmia was observed alongside advanced lens degeneration and corneal abnormalities [111,112]. Additionally, mutations in *lamb1* and *lamc1* have been associated with corneal malformations, as well as disruptions in retinal lamination, suggesting broader roles for these laminin subunits in ocular development beyond the lens [111].

Table 1 provides a comprehensive summary of the mutations in Collagen IV and Laminin-1, their affected ocular tissues, functional consequences, type of evidence, and associated clinical manifestations.

6. Autoantibodies against laminin-1 and collagen IV in ocular diseases

Autoantibodies directed against laminin-1 and type IV collagen have been identified in a variety of autoimmune disorders, including Rheumatoid Arthritis (RA) [113], systemic sclerosis or scleroderma [114], Raynaud's syndrome [115], Buerger's disease [116], and Systemic Lupus Erythematosus (SLE) [117], among others. These autoantibodies are frequently detected in serum, but their direct association with ocular manifestations remains a subject of ongoing research.

The mechanisms through which these autoantibodies contribute to ocular disease involve several key processes. Firstly, autoantibodies can activate the complement system, leading to endothelial injury and disruption of the basement membrane. This disruption increases the permeability of ocular tissues, allowing inflammatory cells to infiltrate and exacerbate tissue damage. In the retina, for example, this can result in retinal vasculitis and retinal pigment epithelial dysfunction, which are commonly observed in autoimmune retinopathies [118].

Moreover, the binding of autoantibodies to basement membrane components may impair cell adhesion and migration, crucial processes in maintaining the integrity of ocular tissues. In the cornea, for example, disrupted integrin-mediated adhesion to the epithelial basement membrane has been shown to delay epithelial migration and promote breakdown of the epithelial layer [119].

Rheumatoid arthritis provides a clear example of these mechanisms in action. This chronic systemic autoimmune disease is primarily characterized by persistent inflammation of synovial joints, leading to cartilage and bone destruction, joint deformities, and functional impairment [120]. Ocular manifestations are common in RA and may serve as early indicators of disease. The most prevalent ophthalmic complication is keratoconjunctivitis sicca (dry eye syndrome) due to lacrimal gland dysfunction [121,122]. Additional ocular pathologies associated with RA include episcleritis (inflammation of the episcleral connective tissue) and scleritis (inflammation of the scleral tissue), both of which may be accompanied by corneal involvement such as peripheral ulcerative keratitis, sclerosing keratitis, filamentary keratitis, and other keratopathies [122–124]. Furthermore, anterior uveitis, posterior segment alterations (e.g., macular edema or disruption), and cataracts have also been reported [124]. Cataract formation in RA patients is often associated with prolonged systemic corticosteroid therapy, which remains a mainstay in RA management [123,125,126].

Furthermore, the presence of circulating autoantibodies targeting type IV collagen and laminin has also been reported in patients with systemic sclerosis (SSc) [114,127]. SSc is a chronic multisystem connective tissue disorder of unknown ethology, primarily characterized by progressive dermal fibrosis, microvascular dysfunction, and visceral

organ involvement [128]. A wide range of ocular manifestations has been documented in SSc patients [129,130], with the most frequent being dry eye disease (keratoconjunctivitis sicca) [131]. Additional ophthalmologic findings include eyelid abnormalities such as skin stiffness, telangiectasias, and blepharitis; corneal pathologies including keratoconus; and retinal vascular changes such as cotton wool spots, intraretinal haemorrhages, hard exudates, and increased vascular tortuosity [132], and retinal lesions like cotton wool spots, intraretinal haemorrhage, and hard exudates, vascular tortuosity [133].

Raynaud's syndrome, often referred to as Raynaud's phenomenon (RP) when secondary to systemic disease, is a vascular disorder characterized by episodic vasospasm of the digital arteries in response to cold or emotional stress. Secondary RP is highly prevalent in patients with SSc, representing one of its earliest clinical signs [134,135]. Autoantibodies against BM components, specifically type IV collagen and laminin, have also been detected in the serum of individuals with RP [115]. The hallmark clinical feature of RP is a triphasic colour change in the extremities (white, blue, and red), with the initial pallor phase colloquially termed "white finger disease" or "corpse finger disease" due to the transient ischemia [136].

Recent studies have identified significant ocular vascular alterations in RP, particularly affecting the choroidal circulation. Optical coherence tomography has revealed reduced choroidal thickness in both primary and secondary RP patients [137,138]. In primary RP, thinning was observed predominantly in the outer nasal and temporal choroidal regions, whereas in secondary RP (typically associated with SSc), thinning was more pronounced in both inner and outer nasal areas. Furthermore, reductions in central foveal thickness and ganglion cell complex (GCC) average values were reported in both groups, indicating possible neurovascular involvement [138].

A variety of additional ocular complications have been described in patients with Raynaud's phenomenon and related systemic vasculopathies. These include papilledema, retinal haemorrhages, irregularities in retinal vessel calibre [139], central retinal artery spasm [135,140], and narrowing of the central retinal artery lumen [141]. Transient corneal opacification accompanied by conjunctival vascular changes has also been observed in individuals with Raynaud's disease following cold exposure, suggesting temperature-sensitive vascular reactivity at the ocular surface [142].

Buerger's disease (BD), also known as thromboangiitis obliterans, is a rare, non-atherosclerotic, inflammatory vasculopathy that predominantly affects small- and medium-sized arteries and veins of the extremities [143]. Its pathogenesis is thought to involve autoimmune mechanisms targeting vascular components, including the production of anti-type IV collagen antibodies [116]. Several studies have identified ocular manifestations associated with BD. Retinal artery occlusion is among the most commonly reported complications, sometimes occurring in conjunction with normal-tension glaucoma [144–146] or with atherosclerotic hypertensive grade I and II retinopathies [147].

Histopathological findings by Marchesani [148] has shown that vessel lumens were narrowed and obliterated in the retina, and ciliary body in patients with BD. The author suggested that narrowing was due to the overgrowth of the fibrous tissue which obliterated the lumen of the vessel.

On the other hand, in a recent case report, Zaoui et al. [149] have observed diffuse choroidal lesions with macular involvement, bulbar conjunctivitis, retinal arterial occlusion, ischemic papilledema, bilateral Granulomatous Keratic precipitates as well as uveitis related to BD. Retinal and vitreous haemorrhages have also been documented [150], as well as anterior ischemic optic neuropathy in patients with BD [151,152].

Systemic Lupus Erythematosus (SLE) is a chronic, autoimmune, multisystem disorder primarily affecting connective tissue [153]. Ocular involvement in SLE is common and can affect nearly every part of the eye [154,155]. Among the most frequent manifestations are keratoconjunctivitis sicca (dry eye syndrome), resulting from lacrimal gland involvement [156]; blepharoconjunctivitis often associated with Meibomian gland dysfunction and chronic inflammation [157]; and lupus retinopathy, which is characterized by cotton-wool spots, intraretinal haemorrhages, and increased vascular tortuosity indicative of microvascular damage [158]. Neurologic complications may also manifest as ocular motility disturbances, such as ocular motor nerve palsies and internuclear ophthalmoplegia, commonly attributed to ischemic microvascular disease of the brainstem [159]. Additionally, the chronic use of corticosteroids in SLE patients contributes to the development of posterior subcapsular cataracts [160].

Table 2
Distribution of type IV collagen and laminin-1 in ocular tissues and associated pathologies.

Ocular structure	Type IV collagen distribution/ function	Laminin-1 distribution/ function	Related pathologies/ notes
Cornea	Present in epithelial BM, Bowman's layer, stroma, Descemet's membrane; provides tensile strength and transparency	Localized in epithelial BM and Descemet's membrane; promotes epithelial adhesion and wound healing	Corneal opacities, dystrophies, keratopathies in collagen IV or laminin defects
Lens	Synthesized by epithelial and fibre cells; major component of lens capsule ensuring elasticity and barrier function	Found throughout lens capsule; regulates epithelial and fibre cell differentiation	Lens dysplasia, anterior lenticonus, cataracts (COL4A1, LAMA1 mutations)
Retina	Present in ILM, Bruch's membrane, and vascular BMs; supports Müller cells and vascular integrity	Expressed in ILM, GCL, INL; guides retinal axons and supports photoreceptor development	Retinal dysgenesis, abnormal vascularization, photoreceptor dysfunction
Optic Nerve	Localized in lamina cribrosa and astrocyte BMs; provides mechanical support to axons	Expressed along optic nerve and in glial BMs; guides RGC axon growth	Optic nerve hypoplasia, glaucoma, axonal degeneration
Iris / Ciliary Body / Trabecular Meshwork	All α chains detected in BMs; maintain barrier and filtration properties	Present in epithelial BMs; involved in aqueous humour regulation	Iridocorneal adhesions, elevated IOP, glaucoma

Goodpasture syndrome [161] another rare but severe autoimmune condition characterized by rapidly progressive glomerulonephritis and pulmonary haemorrhage. The disease is mediated by autoantibodies targeting the non-collagenous (NC1) domain of the α3 chain of type IV collagen [162]. In a clinical study conducted by Jampol et al. [163] immunoglobulin G (IgG) deposits were observed in a linear pattern along Bruch's membrane and the BMs of the choroidal vasculature. Associated ocular findings included areas of choroidal ischemia and non-rhegmatogenous retinal detachments. Clinically, Goodpasture's syndrome may present with cotton-wool spots and branch retinal arteriolar occlusions, with or without infarction of the retinal tissue [164].

Sjögren's syndrome (SjS) is a chronic, systemic autoimmune disorder primarily characterized by lymphocytic infiltration and progressive dysfunction of the exocrine glands, most notably the lacrimal and salivary glands, leading to sicca symptoms [165]. Multiple studies have reported altered expression and distribution of ECM components, including type IV collagen and laminin-1, within the basal lamina of ductal and acinar epithelial cells in both salivary and lacrimal tissues of SjS patients [166,167]. Ocular involvement is frequent and represents one of the hallmark features of the disease. The most prevalent

Table 3
Summary of genetic and autoimmune diseases associated with type iv collagen and laminin-1.

Protein	Disease/syndrome	Type of alteration	Ocular manifestations	Mechanism	References
Type IV Collagen	Anterior Segment Dysgenesis, Glaucoma (COL4A1/COL4A2)**[a]	Genetic mutation	Corneal opacity, iris adhesions, optic nerve hypoplasia	ER stress, BM disruption	[77–84]
	Alport Syndrome (COL4A3, COL4A4, COL4A5)	Genetic mutation	Anterior lenticonus, fleck retinopathy, maculopathy	Loss of α3α4α5 network	[88–96]
	Walker-Warburg Syndrome	Genetic mutation	Retinal dysplasia, microphthalmia, glaucoma	Abnormal BM assembly	[97–99]
	Goodpasture's Syndrome	Autoantibodies (anti-α3 (IV) NC1)	Retinal ischemia, detachment	Autoimmune BM attack	[159–162]
	Rheumatoid Arthritis	Autoantibodies	Keratoconjunctivitis sicca, scleritis, keratitis	Immune-mediated BM damage	[118–124]
	Systemic Sclerosis / Raynaud's	Autoantibodies	Dry eye, retinal vascular changes	Vascular fibrosis, BM autoimmunity	[114–136]
	Buerger's Disease	Autoantibodies	Retinal artery occlusion, uveitis	Vasculitis with anti-collagen IV antibodies	[141–150]
Laminin-1	LAMA1 / LAMB1 / LAMC1 mutations	Genetic mutation	Lens dysplasia, retinal lamination defects, microphthalmia	Impaired ILM and lens capsule formation	[100–112]
	Sjögren's Syndrome	Autoantibodies	Dry eye, corneal melting	Altered laminin in lacrimal BM	[163–170]
	Systemic Lupus Erythematosus	Autoantibodies	Retinopathy, dry eye, cataracts	Immune complex deposition in ocular BM	[151–158]

[a] ** Refers to a spectrum of ocular phenotypes (including anterior segment dysgenesis, optic nerve hypoplasia, and glaucoma) associated with *COL4A1* and *COL4A2* mutations as described in multiple studies [77–84]

manifestation is keratoconjunctivitis sicca (dry eye disease) [168], although more severe extraglandular ocular complications have also been documented. These include sterile corneal melting or necrosis, particularly in individuals with long-standing dry eye syndrome [169,170], as well as uveitis [171], and optic neuropathy [172].

Although anti-collagen IV and anti-laminin-1 antibodies are present in systemic autoimmune diseases, the correlation between their presence and specific ocular manifestations varies. For instance, while rheumatoid arthritis patients frequently exhibit these autoantibodies, only a subset experiences ocular involvement, such as dry eye or scleritis. On the other hand, systemic lupus erythematosus is associated with a higher frequency of ocular manifestations, including uveitis and retinal vasculitis, particularly in patients who test positive for anti-laminin-1 antibodies.

Experimental studies have investigated therapeutic strategies targeting these autoantibodies. In preclinical models of autoimmune uveitis, complement inhibitors have been shown to reduce ocular inflammation, while immunosuppressive therapies, including biologic agents targeting specific inflammatory pathways, are being evaluated for their potential to mitigate ocular damage in autoimmune diseases. Additionally, recent approaches using immune-modulating nanoparticles have demonstrated promising results in controlling ocular inflammation and modulating autoimmune responses, suggesting potential translational applications for autoimmune eye disorders [173].

A summary of diseases associated with genetic and autoimmune alterations in type IV collagen and laminin-1 is presented in Tables 2 and 3, providing an overview of their clinical impact on ocular and systemic pathologies.

7. Conclusions

The ECM, particularly BM components such as type IV collagen and laminin-1, plays fundamental structural and signalling roles in the development, maintenance, and function of ocular tissues. These macromolecules are essential for the organization and integrity of the cornea, lens, retina, and optic nerve, mediating crucial biological processes such as cell adhesion, polarity, migration, and differentiation.

Mutations in genes encoding type IV collagen (e.g., *COL4A1*, *COL4A2*) and laminin subunits (e.g., *LAMA1*, *LAMB1*, *LAMC1*) are associated with a broad spectrum of congenital and degenerative ocular diseases. These include anterior segment dysgenesis, lens dysplasia, retinal vascular malformations, and optic nerve hypoplasia. Likewise, autoimmune responses targeting collagen IV and laminin-1 have been implicated in systemic disorders with ocular involvement, such as systemic lupus erythematosus, Sjögren's syndrome, rheumatoid arthritis, systemic sclerosis, Raynaud's phenomenon, Goodpasture's syndrome, and Buerger's disease, where pathological alterations in BM composition or the presence of autoantibodies contribute to manifestations such as dry eye, uveitis, corneal opacity, retinal ischemia, and optic neuropathy.

In summary, type IV collagen and laminin-1 are essential ECM components required for normal ocular architecture and function. Their precise spatial distribution and tightly regulated expression are fundamental for the integrity of all BMs of the eye. Disruptions due to genetic mutations or immune-mediated mechanisms lead to a wide range of vision-threatening diseases. These findings reinforce the critical role of BM proteins in ocular physiology and highlight their potential as diagnostic biomarkers and therapeutic targets in ocular pathology.

CRediT authorship contribution statement

Ouafa Sijilmassi: Writing – review & editing, Writing – original draft, Methodology, Investigation, Conceptualization.

Declaration of competing interest

The author declares that she has no known competing financial interests or personal relationships that could have influenced the work reported in this paper.

Data availability

No data was used for the research described in the article.

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